REMARKS

Upon entry of this amendment, Claims 1-5, 7-24, and 27-68 constitute the pending claims in the present application. Among them, Claims 2, 17-20, 36-55, and 57-68 are directed to non-elected invention, and are withdrawn from further consideration. Applicants will cancel these claims upon indication of allowable subject matter. Claims 6, 25, and 26 are canceled without prejudice as a result of claim amendment. Applicants reserve the rights to prosecute clams of identical or similar scope as the original claims in one or more future continuation or divisional applications.

Applicants have amended Claims 1, 21, and 56 and their dependent claims to clarify the subject matter claimed. Support can be found throughout the specification, including the original claims. See, for example, page 20, first full paragraph, and original Claims 6 and 26. Applicants submit that no new matter is introduced due to these amendments.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim rejections under 35 U.S.C. § 101

Claims 1, 3-16, 21-35, and 56 are rejected under 35 U.S.C. § 101, because the claimed invention is allegedly directed to non-statutory subject matter. Specifically, the Office Action argues that the claimed invention does not include a physical transformation step. The Office Action further argues that the claimed invention does not produces a tangible result.

While not acquiescing in the reasoning of the Office Action and solely to advance prosecution, Applicants have amended independent Claims 1, 21, and 56 to introduce a step that requires "physical transformation," *i.e.*, testing the engineered polypeptides for activity, thereby obviating the non-statutory subject matter rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. § 112, first paragraph - enablement

Claims 1, 3-16, 21-35, and 56 remain rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In essence, as in the previous Office Action, the instant Office Action relies on Ginalski, and argues that protein structure prediction is only reliable when there is a high degree of sequence homology between the catalytic motif and the replaced set of amino acids in a recipient polypeptide.

Applicants reiterate that the this rationale is based on a misunderstanding of the Ginalski reference and the claimed invention. In addition, Applicants have amended the independent claims to limit the motif to a "protease motif." Thus, the analysis of the *Wands* factors is incorrect, at least with respect to the current pending claims as amended.

The thrust of the enablement rejection is based on the notion that it is difficult to reliably predict the structure / fold of an engineered protein, because "predicted structures can be used only if very close homologs with known structures are available." See, for example, paragraph "e)" on page 6 of the instant Office Action. To support this view, the Office Action cited Ginalski, which suggests that protein structural prediction from primary sequence information "can be used if very close homologs with known structure are available."

However, the claimed invention does not call for protein structural prediction *de novo* from primary sequence information, *i.e.*, amino acid sequence information alone. Instead, as an initial inquiry, the methods of the invention only ask whether the engineered recipient polypeptide still has a similar structure as the wild-type recipient, which are nearly identical to each other except for the few replaced residues.

For example, if a serine protease triad is to be engineered into a recipient polypeptide, at most three amino acids of the recipient polypeptide needs to be replaced initially (if, in the worst case scenario, none of the three amino acids in the serine protease triad matches the target site amino acids on the recipient). In other words, for a small recipient polypeptide of

about 100 residues (or about 11 kDa), the engineered recipient polypeptide will be at least 97% identical to the wild-type recipient polypeptide. Even if up to 10 residues must be replaced in the recipient polypeptide to "graft" in a different protease motif, the 90% sequence identity (between the wild-type recipient and the engineered recipient) usually well exceeds the minimal sequence identity required for reliable structure prediction. In that sense, the cited Ginalski reference in fact supports the enablement of the claimed methods, because Ginalski admits that the traditional protein structure prediction based on sequence homology (also known in the art as "homology modeling") is "of practical importance" (cited in page 6 of the instant Office Action). In other words, Ginalski seems to admit that proteins structures can be reliably predicted if the two proteins share significant sequence identity, which is the case here when comparing the wild-type recipient polypeptide with the engineered recipient polypeptide.

The Office Action seems to suggest that there must be "a high degree of homology between the catalytic motif and the replaced set of amino acids in a recipient polypeptide." Applicants submit that this is a misunderstanding of homology modeling. For homology modeling to work, it is the *overall* sequence homology, rather than the sequence homology between *the residues replaced*, that must share a certain degree of sequence homology. For example, if proteins A and A' both have 100 residues, with 90 being common, they share 90% overall sequence identity. Thus proteins A and A' likely have very similar structure due to the high overall sequence identity. However, if the interpretation of the Office Action is true, proteins A and A' have 10 residues that are, by definition, not identical (*i.e.*, proteins A and A' does not share a high degree of homology in regions consisting of these 10 residues). Thus homology modeling will probably never work if it requires a high degree of sequence homology between residues that have different sequences (*i.e.*, the 10 residues in the hypothetical example above).

In addition, Applicants reiterate that the spatially conserved protease motif residues are usually (but not necessarily) non-consecutive amino acids, such as in the serine protease triad case. Thus the impact of each substitution on its local environment is expected to be relatively independent, at least as compared to the impact of replacing a stretch of consecutive amino acids.

Finally, since multiple rotamers are usually available for each residue to be substituted into a recipient polypeptide, the side-chains of these substituting residues are not rigid / inflexible. Thus minor clashes with the other recipient polypeptide atoms (such as other binding pocket or catalytic pocket atoms) may be avoided by choosing the right rotamer (*see*, for example, Example 2 and Figure 2), while major clashes may result in discarding the individual models with such clashes.

Particularly, pages 19-20 of the instant specification set forth details regarding how to screen out rotamers that tend to clash with the other atoms in the engineered recipient polypeptide.

In summary, the cited art actually supports the enablement of the claimed invention. Applicants submit that a skilled artisan need not conduct any undue experimentation, because the recipient polypeptide of the claimed invention can well tolerate the minimal perturbations to its overall structure. This is partly due to the extremely high overall sequence identity between the recipient polypeptide and the engineered polypeptide, the usually dispersed locations of the residues to be substituted in the recipient polypeptide, the flexibility of the substituting residue side-chains, especially the requirement that the second set of amino acid residues in the recipient polypeptide "have a geometric relationship that matches the spatially conserved geometry" of the motif to be "grafted" onto the recipient polypeptide.

Thus, the claimed invention is fully enabled. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance. Applicants believe no additional fee other than the THREE-month extension fee is due with this response. However, if any additional fee is due in connection with the filing of this response, please charge our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **COTH-P01-002**.

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Respectfully submitted,

By_____

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